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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,513	05/01/2001	Edward F. Delong	MBA-101	7869

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 01/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,513	DELONG ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2005 and 07 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-44* is/are pending in the application.

4a) Of the above claim(s) *8-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7 and 37-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to amendments filed August 25, 2005 and November 7, 2005. Claims 1-44 were previously pending, with claims 8-36 withdrawn from consideration. Applicants amended claims 1, 2, 4-7 and 37-44. Claims 1, 2, 4-7 and 37-44 will be examined, claims 8-36 are withdrawn from consideration.

2. Applicants' amendments overcame the rejection of claims 1, 5 and 37-44 under 35 U.S.C. 112, second paragraph. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" below. The rejections are modified to account for claim amendments.

Response to Arguments

3. Applicant's arguments filed September 25, 2005 have been fully considered but they are not persuasive.

A) Regarding the rejection of claim 7 under 35 U.S.C. 112, first paragraph, written description, based on the lack of proper deposit, Applicants argue that a statement cited by the examiner that the specification should contain a reference to a deposit being made under the terms of the Budapest treaty and that all restrictions imposed by the depositor on the on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements, according to 37 C.F.R. 1.808, is not necessary, citing a statement from MPEP 2406.01 about Ludnak patent, arguing that the statement in the Ludnak patent does not require either the reference to the Budapest Treaty or a statement about deposit maintainence and availability.

However, even putting aside whether a specific statement that the deposit was made under the term of the Budapest Treaty is required, there is one crucial requirement present in the rejection

previously presented, and that is the requirement that the restrictions on the deposited material be irrevocably removed upon granting of the patent (MPEP 2404.01):

"The mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception (37 C.F.R. 1.808(b) that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. *Ex parte Hildebrand*, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990)."

And 37 C.F.R. 1.808(b):

§ 1.808 Furnishing of samples.

(a) A deposit must be made under conditions that assure that:

(1) Access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Director to be entitled thereto under and § 1.14 and 35 U.S.C. 122, and

(2) Subject to paragraph (b) of this section, all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent.

Therefore, Applicants are required to furnish a statement that all restrictions on the accessibility of the deposited material will be irrevocably removed by the applicant upon the granting of the patent.

Since Applicants have furnished no such statement, the rejection is maintained, now for claims 1, 2, 4-7 and 37-44.

Applicants are encouraged to contact my SPE, Gary Benzion, regarding this matter, as he is a designated POC for the USPTO in matters of biological deposits.

B) Regarding the rejection of claims 1-6 and 37-44 under 35 U.S.C. 112, first paragraph, written description, Applicants argue that the specification states clearly that proteorhodopsins are "rhodopsin-like" in that the have seven transmembrane proteins and a retinal binding pocket, therefore defining proteorhodopsin gene as a gene retrieved from naturally occurring bacteria that encodes a protein with seven transmembrane domains and a retinal binding pocket. Applicants argue that amendments to claim 1 make the rejection moot.

However, first, there is no definition of the term "proteorhodopsin" in the specification, the definition understood as a statement in the form "proteorhodopsin is...", "the term "proteorhodopsin" means..." or "the term "proteorhodopsin" refers to...". Absent such statements, the description in the specification does not provide the definition of the term. Further, the presence of the transmembrane helices or a retinal binding pocket is not an indicator of what the function of the protein is, i.e., is it a proton pump, chloride pump, etc. Therefore, since the newly amended claim 1 lacks a functional limitation which limits a genus of possible proteins, the rejection is maintained.

C) Regarding the rejection of claims 1, 2, 5 and 37 under Kitajima et al., Applicants argue that the rhodopsin-like protein of Kitajima et al. is only distantly related in terms of the sequence to the proteorhodopsins of the present invention, and is structurally different as well. Applicants further argue that archeal rhodopsins such as the one of Kitajima et al. must be expressed in their natural organisms to be fully functional, whereas proteorhodopsins can be expressed in E. coli, for example.

Regarding sequence similarity, Applicants claim a DNA molecule comprising a nucleotide sequence encoding a proteorhodopsin protein with at least 78% amino acid sequence identity to SEQ ID NO: 7. According to TC 1600 guidelines, the term "comprising a nucleotide sequence" is interpreted as any nucleic acid that comprises any portion of that nucleic acid sequence, i.e., a dinucleotide. Therefore, since the amino acid sequence of the proteins of Kitajima et al. contains several regions of homology where two amino acids are identical to the amino acids of the proteorhodopsin with SEQ ID NO: 7, the corresponding nucleic acid sequence would be identical to within a dinucleotide. Further, the structure of the protein of Kitajima et al. also has seven transmembrane helices (see Fig. 1), however, this feature is not critical for the purpose of comparing sequences of nucleic acids, as is the fact that proteins of Kitajima et al. cannot be expressed in E. coli (no such statement exists in the paper of Kitajima et al.).

The rejection is maintained.

D) Regarding the rejection of claims 6, 39 and 41 under 35 U.S.C. 103(a) over Kitajima et al. and Shimono et al., the rejection of claims 40 and 42 under 35 U.S.C. 103(a) over Kitajima et al. and Shimono et al., in view of Zozulya et al., the rejection of claim 43 under 35 U.S.C. 103(a) over Kitajima et al. and Shimono et al., in view of Mollaaghababa et al., the rejection of claim 44 under 35 U.S.C. 103(a) over Kitajima et al., Shimono et al., and Mollaaghababa et al. in view of Zozulya et al., Applicants argue that since the rejection of claim 1 over Kitajima et al. is improper, so are these rejection. The issue of the rejection of claim 1 was addressed above.

The rejections are maintained.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, 4-7 and 37-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification. The genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named SEQ ID Nos (4, 8, 10, 12, ...62, 64; 30 sequences total). Thus, applicant has express possession of only 30 sequences of rhodopsin genes, in a genus which comprises of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided. Further, these claims encompass allelic variants including insertions and mutations, and only specific nucleic acid sequences have been provided. No written description of alleles, of

upstream or downstream regions containing additional sequence has been provided in the specification.

Applicants amended the claims to recite an isolated DNA molecule comprising a nucleotide sequence encoding a proteorhodopsin protein with at least 78% sequence identity to SEQ ID NO: 7. SEQ ID NO: 7 has 249 amino acids, therefore the 22% of unspecified amino acid sequence constitutes 54 amino acids. Therefore, the number of possible protein molecules is 54^{20} or about $4x\ 10^{34}$ sequences. Translating this into nucleic acid sequences, 54 amino acids are encoded by a minimum of 54x3 = 162 nucleotides, with 162^4, or about 6.9×10^8 nucleotide sequences, and this not counting alternative codon usage, point mutations, insertions, deletions, etc. Therefore, the total minimum number of nucleic acid sequences is about 28×10^{42}. The limitations of the protein possessing seven transmembrane helices and retinol binding pocket are not structural limitations, i.e., any of the proteins differing by up to 22% in their amino acid sequence could still have seven transmembrane helices and a retinal binding pocket, but a very different function. For example, as described by Ihara et al. (J. Mol. Biol., vol. 285, pp. 163-174, 1999), rhodopsin proteins isolated from archea all have seven transmembrane helices and bind retinal, but four different types of functions, namely, proton pumps, chloride ion pumps and two types of sensory proteins (Abstract; Fig. 1; page 164, fourth and fifth paragraph). Therefore, a limitation of a protein possessing certain structure does not automatically imply protein function.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the

> patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the proteorhodopsin gene lacks any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the 30 specific sequences, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to "an isolated DNA molecule comprising a nucleotide sequence encoding a proteorhodopsin protein with at least 78% sequence identity to SEQ ID NO: 7", for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise sequences with SEQ ID NO: 4, 8, 10, 12, ...62 and 64. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

6. Claims 1, 2, 4-7 and 37-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The deposit of cells containing clone BAC31A8 has been noted in this application (see, for example, page 52). While the specification teaches the sequence of a 750 bp insert (i.e. SEQ ID NO: 4) present in clone BAC31A8 and a 747 bp insert of SEQ ID NO: 6, the specification does not teach the complete sequence of the BAC vector. Because the sequence of the clone BAC31A8 is not known and because it is not clear whether BAC31A8 is known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the gene product of claims 1, 2, 4-7 and 37-44 require the use of clone BAC31A8, a suitable deposit for patent purposes is required. Without the publicly available deposit of the above clone, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed.

According to MPEP 2404.01:

"The mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception (37 C.F.R. 1.808(b) that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. *Ex parte Hildebrand*, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990)."

And 37 C.F.R. 1.808(b):

§ 1.808 Furnishing of samples.

(a) A deposit must be made under conditions that assure that:

(1) Access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Director to be entitled thereto under and § 1.14 and 35 U.S.C. 122, and

(2) Subject to paragraph (b) of this section, all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent.

Therefore, Applicants are required to furnish a statement that all restrictions on the accessibility of the deposited material will be irrevocably removed by the applicant upon the granting of the patent to overcome this rejection.

Claim interpretation

7. The following interpretations are used for the purpose of art rejections:

A) The term "proteorhodopsin" is not defined in the specification, therefore it is interpreted as referring to any rhodopsin.

B) In claim 1, the phrase "an isolated DNA molecule comprising a nucleotide sequence encoding a proteorhodopsin protein with at least 78% sequence identity to SEQ ID NO: 7" is interpreted as any nucleic acid which has at least two nucleotides in common with a nucleic acid encoding SEQ ID NO: 7. According to TC 1600 guidelines, the term "comprising a nucleotide sequence" is interpreted as any nucleic acid that comprises any portion of that nucleic acid sequence, i.e., a dinucleotide.

C) In claim 39, the phrase "for producing said proteorhodopsin protein in a host" is treated as an intended use of the product, and therefore not taken into account when the claim is compared with the prior art.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 2, 5 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Kitajima et al. (Biochem. Biophys. Res. Comm., vol. 220, pp. 341-345, 1996; cited in the previous office action).

Regarding claim 1, Kitajima et al. teach a proteorhodopsin gene comprising an isolated DNA sequence for encoding a proteorhodopsin protein (Kitajima et al. teach genes encoding three rhodopsins: cR-3, chR-3 and csR-3 (Abstract; page 342, paragraphs 6, 7, 8; page 343, paragraphs 1, 2; Fig. 1). For example, amino acids 13 and 14 and 20 and 21 of the protein cR1 are LG, they are identical to amino acids 7 and 8 of SEQ ID NO: 7. Taking into account that possible codons for leucine are CTX and TTA or TTG, and possible codons for glycine are GGX, where X= A, T, C or G, a nucleic acid encoding a cR1 protein has at least one dinucleotide identical to a sequence encoding an amino acid sequence of SEQ ID NO: 7.)

Regarding claim 2, Kitajima et al. teach that the genes were retrieved from genomic fragments of naturally occurring marine bacteria *Haloarcula vallismortis* (page 341, the last paragraph; page 344, third paragraph).

Regarding claim 5, Kitajima et al. teach retrieval of the genes from a recombinant Sac I library (page 344, paragraph 7).

Regarding claim 37, Kitajima et al. teach amplification by polymerase chain reaction (page 344, third paragraph).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 6, 39 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitajima et al. (Biochem. Biophys. Res. Comm., vol. 220, pp. 341-345, 1996; cited in the previous office action) and Shimono et al. (FEBS Letters, vol. 420, pp. 54-56, 1997; cited in the previous office action).

A) Claim 39 is drawn to the isolated nucleic molecule of claim 1, wherein said nucleic acid molecule is placed in an expression vector for producing said proteorhodopsin protein in a host. Claim 41 is drawn to the nucleic molecule of claim 39, wherein the host is a bacterium. Claim 6 is drawn to the nucleic molecule of claim 41, where the bacterium is E. coli.

B) Kitajima et al. teach rhodopsin genes obtained from marine environment, namely, from a marine bacterium *Haloarcula vallismortis* (page 220, the last paragraph). Kitajima et al. do not teach placing the genes in bacterial expression vectors.

C) Shimono et al. teach placing a gene encoding a rhodopsin from *Natronobacterium pharaonis* into an expression vector pET21c for expression in a bacterium host, E. coli (page 54, paragraphs 5 and 6).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have cloned the rhodopsin genes of Kitajima et al. into an expression vector of Shimono et al. The motivation to do so, provided by Shimono et al., would have been that

expression of rhodopsin in E. coli allowed investigation of photochemical properties of rhodopsins using site-directed mutagenesis (page 56, the last paragraph).

12. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kitajima et al. (Biochem. Biophys. Res. Comm., vol. 220, pp. 341-345, 1996; cited in the previous office action) and Shimono et al. (FEBS Letters, vol. 420, pp. 54-56, 1997; cited in the previous office action), as applied to claim 39 above, and further in view of Zozulya et al. (Protein Eng., vol. 3, pp. 453-458, 1990; cited in the previous office action).

A) Claim 40 is drawn to the nucleic molecule of claim 39, wherein the host is an artificial membrane system.

B) Neither Kitajima et al. nor Shimono et al. teach the host being an artificial membrane system.

C) Zozulya et al. teach expression of rhodopsin in cell-free translation system supplemented with artificial membranes, phosphatidylcholine liposomes (page 453, the last paragraph; page 454, first and second paragraphs).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used artificial membranes of Zozulya et al. for placing a rhodopsin expression vector of Kitajima et al. and Shimono et al. The motivation to do so, as stated by Zozulya et al., would have been that "... The other obvious advantage of preparative cell-free expression system, as compared to the alternative ones, include: experimental simplicity and speed, the possibility of obtaining easily protein labeled with radioactive or modified amino acids, the possibility of inserting a membrane protein in a desired lipid environment co-translationally and, last but not least, comparatively low price of an experiment." (page 457, the last paragraph).

13. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kitajima et al. (Biochem. Biophys. Res. Comm., vol. 220, pp. 341-345, 1996; cited in the previous office action) and Shimono et al. (FEBS Letters, vol. 420, pp. 54-56, 1997; cited in the previous office action), as applied to claims 39 and 41 above, and further in view of Zozulya et al. (Protein Eng., vol. 3, pp. 453-458, 1990; cited in the previous office action).

A) Claim 42 is drawn to the nucleic molecule of claim 41, wherein the host is a cell membrane preparation of a bacterium.

B) Neither Kitajima et al. nor Shimono et al. teach the host being an artificial membrane system.

C) Zozulya et al. teach expression of bovine rhodopsin in cell-free translation system supplemented with artificial membranes, phosphatidylcholine liposomes (page 453, the last paragraph; page 454, first and second paragraphs). Zozulya et al. teach membranes prepared from eukaryotic microsomes of rat brain cortex and dog pancreas (page 454, third paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used membrane preparations of Zozulya et al. for placing a rhodopsin expression vector of Kitajima et al. and Shimono et al. The motivation to do so, as stated by Zozulya et al., would have been that "... The other obvious advantage of preparative cell-free expression system, as compared to the alternative ones, include: experimental simplicity and speed, the possibility of obtaining easily protein labeled with radioactive or modified amino acids, the possibility of inserting a membrane protein in a desired lipid environment co-translationally and, last but not least, comparatively low price of an experiment." (page 457, the last paragraph). Therefore, it would have been obvious to one of ordinary skill in the art to have used bacterial-derived membranes in a system in which bacterial proteins were expressed.

14. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kitajima et al. (Biochem. Biophys. Res. Comm., vol. 220, pp. 341-345, 1996; cited in the previous office action) and Shimono et al. (FEBS Letters, vol. 420, pp. 54-56, 1997; cited in the previous office action), as applied to claim 39 above, and further in view of Mollaaghababa et al. (PNAS, vol. 93, pp. 11482-11486, 1996; cited in the previous office action).

A) Claim 43 is drawn to the nucleic molecule of claim 39, wherein the host is a eukaryote.

B) Neither Kitajima et al. nor Shimono et al. teach placing genes in eukaryotic expression vectors.

C) Mollaaghababa et al. teach expression of bovine rhodopsin in eukaryotic host cells of *Saccharomyces cerevisiae* (Abstract; page 11482, the last paragraph; page 11483, paragraphs 1, 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the yeast cells of Mollaaghababa et al. to express rhodopsins of Kitajima et al. The motivation to do so, provided by Mollaaghababa et al., would have been that expression in yest cells provided properly folded and fully functional rhodopsin (Abstract; page 11486, the last paragraph).

15. Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kitajima et al. (Biochem. Biophys. Res. Comm., vol. 220, pp. 341-345, 1996; cited in the previous office action), Shimono et al. (FEBS Letters, vol. 420, pp. 54-56, 1997; cited in the previous office action) and Mollaaghababa et al. (PNAS, vol. 93, pp. 11482-11486, 1996; cited in the previous office action), as applied to claim 43 above, and further in view of Zozulya et al. (Protein Eng., vol. 3, pp. 453-458, 1990; cited in the previous office action).

A) Claim 44 is drawn to the nucleic molecule of claim 43, wherein the host is a cell membrane preparation of a eukaryote.

B) Neither Kitajima et al. nor Shimono et al. teach the host being an artificial membrane system.

C) Zozulya et al. teach expression of bovine rhodopsin in cell-free translation system supplemented with artificial membranes, phosphatidylcholine liposomes (page 453, the last paragraph; page 454, first and second paragraphs). Zozulya et al. teach membranes prepared from eukaryotic microsomes of rat brain cortex and dog pancreas (page 454, third paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used eukaryotic membrane preparations of Zozulya et al. for placing a rhodopsin expression vector of Kitajima et al. and Shimono et al. The motivation to do so, as stated by Zozulya et al., would have been that "... The other obvious advantage of preparative cell-free expression system, as compared to the alternative ones, include: experimental simplicity and speed, the possibility of obtaining easily protein labeled with radioactive or modified amino acids, the possibility of inserting a membrane protein in a desired lipid environment co-translationally and, last but not least, comparatively low price of an experiment." (page 457, the last paragraph).

16. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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1/20/06